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NEWS 16	MAR 31	CA/CAplus and CASREACT patent number format for U.S. applications updated
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NEWS 22	APR 28	IMSRESEARCH reloaded with enhancements
NEWS 23	MAY 30	INPAFAMDB now available on STN for patent family searching
NEWS 24	MAY 30	DGENE, PCTGEN, and USGENE enhanced with new homology sequence search option
NEWS 25	JUN 06	EPFULL enhanced with 260,000 English abstracts
NEWS 26	JUN 06	KOREAPAT updated with 41,000 documents
NEWS 27	JUN 13	USPATFULL and USPAT2 updated with 11-character patent numbers for U.S. applications
NEWS 28	JUN 19	CAS REGISTRY includes selected substances from web-based collections
NEWS 29	JUN 25	CA/CAplus and USPAT databases updated with IPC reclassification data

NEWS EXPRESS JUNE 27 08 CURRENT WINDOWS VERSION IS V8.3,
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                                                           ENTRY    SESSION
FULL ESTIMATED COST                                          0.21       0.21

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=> e halofuginone
E1            4     HALOFUGI/BI
E2            4     HALOFUGINON/BI
E3            4 --> HALOFUGINONE/BI
E4            2     HALOG/BI
E5            1     HALOGA/BI
E6            1     HALOGABI/BI
E7            1     HALOGABIDE/BI
E8          151     HALOGEN/BI
E9          132     HALOGENASE/BI
E10          10     HALOGENATE/BI
E11          10     HALOGENATED/BI
E12           1     HALOGENE/BI

=> s e3
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L1            4 HALOFUGINONE/BI

=> file caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     5.61       5.82

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FILE COVERS 1907 - 30 Jun 2008  VOL 149 ISS 1
FILE LAST UPDATED: 29 Jun 2008  (20080629/ED)

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reclassification data for the second quarter of 2008.

Effective October 17, 2005, revised CAS Information Use Policies apply.
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http://www.cas.org/legal/infopolicy.html

=> s l1
L2          323 L1

=> s l1 and (liver or hepatocyte)
            323 L1
         592417 LIVER
          38178 LIVERS
         595621 LIVER
                (LIVER OR LIVERS)
          53183 HEPATOCYTE
          46407 HEPATOCYTES
          68647 HEPATOCYTE
                (HEPATOCYTE OR HEPATOCYTES)
L3           47 L1 AND (LIVER OR HEPATOCYTE)

=> s l3 and py<=2002
       22935492 PY<=2002
L4           24 L3 AND PY<=2002

=> d l4 ibib abs 1-24

L4   ANSWER 1 OF 24  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:         2002:600553  CAPLUS
DOCUMENT NUMBER:          138:379131
TITLE:                    Halofuginone, a collagen type I inhibitor improves
                          liver regeneration in cirrhotic rats
AUTHOR(S):                Spira, Gadi; Mawasi, Nidal; Paizi, Melia; Anbinder,
                          Natali; Genina, Olga; Alexiev, Rosaly; Pines, Mark
```

CORPORATE SOURCE: Rappaport Family Institute for Research in the Medical Sciences, The Bruce Rappaport Faculty of Medicine, Department of Anatomy and Cell Biology, Technion, Haifa, Israel
SOURCE: Journal of Hepatology (2002), 37(3), 331-339
CODEN: JOHEEC; ISSN: 0168-8278
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hepatic fibrosis involves excess deposition of extracellular connective tissue of which collagen type I fibers form the predominant component. Left untreated it develops into cirrhosis, often linked with hepatocellular carcinoma. Owing to the fact that cirrhotic liver regeneration is impaired, resection of hepatocellular carcinoma associated with cirrhosis is questionable. The aim of the present study was to determine the potential of halofuginone, a collagen type I inhibitor, in improving liver regeneration in cirrhotic rats. Partial hepatectomy (70%) was performed in thioacetamide-induced cirrhotic rats fed a halofuginone-containing diet. Liver regeneration was monitored by mass and proliferating cell nuclear antigen. The Ishak staging system and hydroxyproline content were used to evaluate the level of fibrosis. Halofuginone administered prior to and following partial hepatectomy did not inhibit normal liver regeneration despite the reduced levels of collagen type I mRNA. When given to rats with established fibrosis, it caused a significant reduction in α smooth muscle actin, TIMP-2, collagen type I gene expression and collagen deposition. Such animals demonstrated improved capacity for regeneration. Thus, halofuginone may prove useful in improving survival of patients with hepatocellular carcinoma and cirrhosis undergoing surgical resection.
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:531106 CAPLUS
DOCUMENT NUMBER: 137:368801
TITLE: Immunoassay and HPLC detection of halofuginone in chicken liver samples obtained from commercial slaughterhouses: a combined study
AUTHOR(S): Beier, Ross C.; Feldman, Steve F.; Dutko, Terry J.; Petersen, H. Delvar; Stanker, Larry H.
CORPORATE SOURCE: Southern Plains Agricultural Research Center, Agricultural Research Service, College Station, TX, 77845-4988, USA
SOURCE: Food and Agricultural Immunology (2002), 14(1), 29-40
CODEN: FAIMEZ; ISSN: 0954-0105
PUBLISHER: Carfax Publishing
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Halofuginone (Hal) is a feed additive used worldwide to prevent coccidiosis in com. poultry production The current regulatory method for determining the action level of Hal residues in poultry involves measuring parent Hal in liver tissue by HPLC. A competitive ELISA (cELISA) for Hal was evaluated with respect to HPLC in determining Hal in 473 samples of chicken liver tissue obtained from com. poultry slaughterhouses. Chicken liver samples were divided, and analyzed by both the US Department of Agriculture, Food Safety and Inspection Service's (FSIS's) regulatory method, and by the US Department of Agriculture, Agricultural Research Service's (ARS's) cELISA method described here. The lower level of detection for Hal was 50 ppb by the FSIS HPLC method and 38 ppb by the ARS cELISA method. The lower cutoff limit for this study was 50 ppb as mandated by FSIS SOP. There was good

agreement in the results obtained by HPLC and cELISA. In addition, the cELISA method does not require the use of organic solvents. These data clearly demonstrate that the cELISA method could be used as a screening method for the anal. of Hal in chicken liver tissue. If the cELISA had been used as a screening tool in this study, then only 6 samples (≥ 100 and < 160 ppb) out of the 473 samples analyzed would have required further anal. by HPLC. The organic solvent waste (over 100 l) generated by the HPLC method would have then been reduced to approx. 1.272 l, a considerable time and cost savings in waste management.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:322906 CAPLUS

DOCUMENT NUMBER: 137:179825

TITLE: Halofuginone, an inhibitor of type-I collagen synthesis and skin sclerosis, blocks transforming-growth-factor-β-mediated Smad3 activation in fibroblasts

AUTHOR(S): McGaha, Tracy L.; Phelps, Robert G.; Spiera, Harry; Bona, Constantin

CORPORATE SOURCE: Department of Microbiology, The Mount Sinai School of Medicine, New York, NY, 10029, USA

SOURCE: Journal of Investigative Dermatology (2002), 118(3), 461-470
CODEN: JIDEAE; ISSN: 0022-202X

PUBLISHER: Blackwell Publishing, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Halofuginone is a drug that has been shown to have an antifibrotic property in vitro and in vivo. Whereas halofuginone shows promise as a therapeutic agent for a variety of diseases including scleroderma, liver cirrhosis, cystic fibrosis, and certain types of cancer, the mechanism of action remains unknown. Using the tight skin mouse (TSK) model for scleroderma, we evaluated the ability of halofuginone to inhibit spontaneous development of dermal fibrosis. We found that administration of a low dose of halofuginone both in adult and newborn animals for 60 d prevented the development of cutaneous hyperplasia (dermal fibrosis). In vitro halofuginone was found to reduce the amount of collagen synthesized by fibroblasts. This effect was due to a reduction in the promoter activity of the type-I collagen genes as treatment of fibroblast cultures with 10-8 M halofuginone reduced the level of α2(I) collagen message detectable by northern blot and greatly reduced the activity of a reporter construct under control of the -3200 to +54 bp α2(I) collagen promoter. In addition, anal. of transforming growth factor β signaling pathways in fibroblasts revealed that halofuginone inhibited transforming-growth-factor-β-induced upregulation of collagen protein and activity of the α2(I) collagen promoter. Further we found that halofuginone blocked the phosphorylation and subsequent activation of Smad3 after transforming growth factor β stimulation. Apparently the inhibitory property was specific to Smad3 as there was no inhibitory effect on the activation of Smad2 after stimulation with transforming growth factor β. Our results demonstrate that halofuginone is a specific inhibitor of type-I collagen synthesis and may elicit its effect via interference with the transforming growth factor β signaling pathway.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:797625 CAPLUS

DOCUMENT NUMBER: 137:118991

TITLE: Pharmacokinetics and tissue distribution of

halofuginone (NSC 713205) in CD2F1 mice and Fischer 344 rats

AUTHOR(S): Stecklair, Kataleeya P.; Hamburger, Deborah R.; Egorin, Merrill J.; Parise, Robert A.; Covey, Joseph M.; Eiseman, Julie L.

CORPORATE SOURCE: Molecular Therapeutics/Drug Discovery Program, University of Pittsburgh Cancer Institute, Pittsburgh, PA, 15213, USA

SOURCE: Cancer Chemotherapy and Pharmacology (2001), 48(5), 375-382
CODEN: CCPHDZ; ISSN: 0344-5704

PUBLISHER: Springer-Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Halofuginone (HF) inhibits synthesis of collagen type I and matrix metalloproteinase-2 and is being considered for clin. evaluation as an antineoplastic agent. Pharmacokinetic studies were performed in the title rodents to define the plasma pharmacokinetics, tissue distribution, and urinary excretion of HF after i.v. delivery and the bioavailability of HF after i.p. and oral delivery. HF was rapidly and widely distributed in rodent tissues and was not converted to detectable metabolites. In mice, HF was 100% bioavailable when given i.p. but could not be detected in plasma after oral administration, suggesting limited oral bioavailability. However, substantial concns. were present in the liver, kidneys, and lungs. HF was present in rat plasma after an oral dose, but the time course and low concns. achieved precluded reliable estimation of bioavailability. These data may assist in designing and interpreting addnl. preclin. and clin. studies of HF.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2001:703740 CAPLUS

DOCUMENT NUMBER: 135:251986

TITLE: Methods for treating fibroproliferative diseases with antiproliferative or antifibrotic agents, especially antisense c-Jun oligonucleotides

INVENTOR(S): Peterson, Theresa C.

PATENT ASSIGNEE(S): Dalhousie University, Can.

SOURCE: U.S., 13 pp., Cont.-in-part of U.S. 6,025,151.
CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 4

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6294350	B1	20010925	US 1999-433621	19991102 <--
US 5985592	A	19991116	US 1997-870096	19970605 <--
US 6025151	A	20000215	US 1998-92317	19980605 <--
WO 2001032156	A2	20010510	WO 2000-IB1731	20001102 <--
WO 2001032156	A3	20020926		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1997-870096 A2 19970605
US 1998-92317 A2 19980605
US 1999-433621 A1 19991102

AB In accordance with the present invention, fibroproliferative disease or condition characterized by such symptoms as increased levels of c-Jun homodimers, increased heterodimerization of c-Jun with another signaling peptide, increased levels of phosphorylated c-Jun, or increased presence of Jun kinase are treated by administering to the subject an amount of a compound effective to ameliorate one or more of the symptoms of the disease or condition, for example, an antiproliferative or antifibrotic agent. Preferred compds. for administration according to the invention are antisense c-Jun oligonucleotides and compds. that block c-Jun phosphorylation, such as pentoxifylline, or a functional derivative or metabolite thereof. Also provided by the present invention are in vitro tests for identifying whether a test compound is useful for treatment of a subject afflicted with such a disease and kits useful for conducting such assays.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:338333 CAPLUS
DOCUMENT NUMBER: 134:357558
TITLE: Methods for treating fibroproliferative diseases
INVENTOR(S): Peterson, Theresa C.
PATENT ASSIGNEE(S): Dalhousie University, Can.
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032156	A2	20010510	WO 2000-IB1731	20001102 <--
WO 2001032156	A3	20020926		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6294350	B1	20010925	US 1999-433621	19991102 <--

PRIORITY APPLN. INFO.: US 1999-433621 A1 19991102
US 1997-870096 A2 19970605
US 1998-92317 A2 19980605

AB In accordance with the present invention, fibroproliferative disease or condition characterized by such symptoms as increased levels of c-Jun homodimers, increased heterodimerization ofc-Jun with another signaling peptide, increased levels of phosphorylated c-Jun, or increased presence of Jun kinase are treated by administering to the subject an amount of a compound effective to ameliorate one or more of the symptoms of the disease or condition, for example, an antiproliferative or antifibrotic agent. Preferred compds. for administration according to the invention are antisense c-Jun oligonucleotides and compds. that block c-Jun phosphorylation, such as pentoxifylline, or a functional derivative or metabolite thereof. Also provided by the present invention are in vitro tests for identifying whether a test compound is useful for treatment of a

subject afflicted with such a disease and kits useful for conducting such assays.

L4 ANSWER 7 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:122373 CAPLUS
DOCUMENT NUMBER: 135:131807
TITLE: Halofuginone to prevent and treat thioacetamide-induced liver fibrosis in rats
AUTHOR(S): Bruck, Rafael; Genina, Olga; Aeed, Hussein; Alexiev, Rosaly; Nagler, Arnon; Avni, Yona; Pines, Mark
CORPORATE SOURCE: Department of Gastroenterology, Agricultural Research Organization, Bet Dagan, 50250, Israel
SOURCE: Hepatology (Philadelphia) (2001), 33(2), 379-386
CODEN: HPTLD9; ISSN: 0270-9139
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hepatic fibrosis is associated with the activation of hepatic stellate cells (HSC), the major source of the extracellular matrix (ECM) proteins. The predominant ECM protein synthesized by the HSC is collagen type I. The authors evaluated the effect of halofuginone - an inhibitor of collagen synthesis - on thioacetamide (TAA)-induced liver fibrosis in rats. In the control rats, the HSC did not express smooth muscle actin, collagen type I gene, or tissue inhibitor of metalloproteinases-2 (TIMP-2), suggesting that they were in their quiescent state. When treated with TAA, the livers displayed large fibrous septa, which were populated by smooth muscle actin-pos. cells expressing high levels of the collagen α1(I) gene and containing high levels of TIMP-2, all of which are characteristic of advanced fibrosis. Halofuginone given orally before fibrosis induction prevented the activation of most of the stellate cells and the remaining cells expressed low levels of collagen α1(I) gene, resulting in low levels of collagen. The level of TIMP-2 was almost the same as in the control livers. When given to rats with established fibrosis, halofuginone caused almost complete resolution of the fibrotic condition. The levels of collagen, collagen α1(I) gene expression, TIMP-2 content, and smooth muscle actin-pos. cells were as in the control rats. Halofuginone inhibited the proliferation of other cell types of the fibrotic liver in vivo and inhibited collagen production and collagen α1(I) gene expression in the SV40-immortalized rat HSC-T6 cells in vitro. These results suggest that halofuginone may become an effective and novel mode of therapy in the treatment of liver fibrosis.
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2000:133423 CAPLUS
DOCUMENT NUMBER: 132:161276
TITLE: Extracellular matrix-regulating compounds, including quinazolinones, for inhibition of pathogenic processes related to tissue trauma
INVENTOR(S): Pines, Mark; Vlodavsky, Israel; Nagler, Arnon; Hazum, Eli
PATENT ASSIGNEE(S): Hadasit Medical Research Services and Development Company Ltd., Israel; Agricultural Research Organization
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

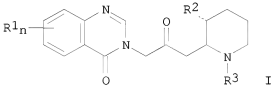
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000009070	A2	20000224	WO 1999-IL440	19990813 <--
WO 2000009070	A3	20001019		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2340176	A1	20000224	CA 1999-2340176	19990813 <--
AU 9951914	A	20000306	AU 1999-51914	19990813 <--
AU 756437	B2	20030116		
EP 1109559	A2	20010627	EP 1999-936952	19990813 <--
EP 1109559	B1	20051026		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002522462	T	20020723	JP 2000-564574	19990813 <--
AT 307586	T	20051115	AT 1999-936952	19990813
ES 2255286	T3	20060616	ES 1999-936952	19990813
US 20070010538	A1	20070111	US 2006-402638	20060411

PRIORITY APPLN. INFO.:			
	IL 1998-125790	A	19980813
	US 1999-137145P	P	19990601
	WO 1999-IL440	W	19990813
	US 2001-762715	B1	20010618

OTHER SOURCE(S): MARPAT 132:161276

GI



I

AB Compns. and methods are provided to prevent the pathogenic aspects of tissue trauma while preserving normal tissue repair mechanisms, based on the fact that these mols. abrogate the cascade of damage initiated by tissue trauma, while maintaining this the requisite healthy extracellular matrix economy. The composition for regulating the extracellular matrix economy, comprise a pharmaceutically effective amount of an effector in combination with a pharmaceutically acceptable carrier. Preferably, the effector is a quinazolinone derivative More preferably, the quinazolinone derivative is I wherein (R1 = H, halo, nitro, benzo, lower alkyl, Ph, lower alkoxy; R2 = OH, acetoxy, lower alkoxy; R3 = H, lower alkenoxy; n = 1, 2) and pharmaceutically acceptable salts thereof. Most preferably, the effector is Halofuginone or a pharmaceutically acceptable salt thereof.

L4 ANSWER 9 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1998:776630 CAPLUS
DOCUMENT NUMBER: 130:20585
TITLE: Treatment of hepatic cirrhosis
INVENTOR(S): Pines, Mark; Nagler, Arnon
PATENT ASSIGNEE(S): Hadasit Medical Research Services and Development, Israel; Agricultural Research Organization; Friedman,

Mark, M.
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9852514	A2	19981126	WO 1998-US10505	19980522 <--
WO 9852514	A3	19990819		
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RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2290502	A1	19981126	CA 1998-2290502	19980522 <--
CA 2290502	C	20070828		
EP 1014988	A2	20000705	EP 1998-924847	19980522 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002515905	T	20020528	JP 1998-550682	19980522 <--
AU 748754	B2	20020613	AU 1998-76922	19980522 <--
IL 132848	A	20040831	IL 1998-132848	19980522

PRIORITY APPLN. INFO.: US 1997-862382 A 19970523
WO 1998-US10505 W 19980522
OTHER SOURCE(S): MARPAT 130:20585
AB A composition for treating hepatic fibrosis and hepatic cirrhosis, and methods of using and manufacturing the composition are provided. The composition includes a quinazolinone derivative, preferably halofuginone. Examples are given showing the effect of halofuginone on histol. and morphol. of rat liver, effect of halofuginone on mild fibrosis in rat liver, inhibition of fibrosis induced by bile duct ligation, and suitable formulations for administration of halofuginone.

L4 ANSWER 10 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1998:548532 CAPLUS
DOCUMENT NUMBER: 129:170518
ORIGINAL REFERENCE NO.: 129:34509a,34512a
TITLE: Quinazolinone-containing pharmaceutical compositions for prevention of neovascularization and for treating malignancies
INVENTOR(S): Pines, Mark; Nagler, Arnon; Vlodavsky, Israel; Miao, Hua-Quan
PATENT ASSIGNEE(S): Agricultural Research Organization, Israel; Hadasit Medical Research Services and Development Company Ltd.
SOURCE: PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9834613	A1	19980813	WO 1998-IL70	19980211 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,				

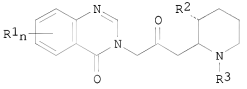
DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

US 6028075	A	20000222	US 1997-797703	19970211	<--
CA 2280850	A1	19980813	CA 1998-2280850	19980211	<--
CA 2280850	C	20040113			
AU 9860049	A	19980826	AU 1998-60049	19980211	<--
AU 738516	B2	20010920			
EP 1007044	A1	20000614	EP 1998-903275	19980211	<--
EP 1007044	B1	20070718			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 2001518075	T	20011009	JP 1998-534077	19980211	<--
IL 131349	A	20040831	IL 1998-131349	19980211	
AT 367158	T	20070815	AT 1998-903275	19980211	
ES 2290983	T3	20080216	ES 1998-903275	19980211	
US 6420371	B1	20020716	US 2000-479660	20000110	<--
US 39574	E1	20070417	US 2000-742993	20001220	

PRIORITY APPLN. INFO.:	US 1997-797703	A	19970211
	WO 1998-IL70	W	19980211

OTHER SOURCE(S): MARPAT 129:170518

GI



I

AB Compns. are provided for attenuating neovascularization and treating malignancies. The compns. include a pharmaceutically effective amount of I (R1 = H, halo, nitro, benzo, lower alkyl, Ph, lower alkoxy; R2 = OH, acetoxy, lower alkoxy; and R3 = H, lower alkenoxy carbonyl), and pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable carrier. Compds. of the invention include Halofuginone and pharmaceutically acceptable salts thereof.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	1998:172859 CAPLUS
DOCUMENT NUMBER:	128:166540
ORIGINAL REFERENCE NO.:	128:32819a,32822a
TITLE:	Detection of Halofuginone Residues in Chicken Liver Tissue by HPLC and a Monoclonal-Based Immunoassay
AUTHOR(S):	Beier, Ross C.; Dutko, Terry J.; Buckley, Sandra A.; Muldoon, Mark T.; Holtzapple, Carol K.; Stanker, Larry H.
CORPORATE SOURCE:	Food Animal Protection Research Laboratory Agricultural Research Service, U.S. Department of Agriculture, College Station, TX, 77845-9594, USA
SOURCE:	Journal of Agricultural and Food Chemistry (1998), 46(3), 1049-1054 CODEN: JAFCAU; ISSN: 0021-8561

PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The quinazolinone halofuginone (Hal) is a feed additive used worldwide to prevent coccidiosis in com. poultry production The current regulatory method for determining the action level of Hal residues in poultry involves measuring parent Hal in liver tissue by HPLC. That procedure is not amenable to high sample throughput due to a complex and tedious sample preparation scheme. A competitive ELISA (cELISA) that can be used as a screening tool for determining Hal in chicken liver tissue is described. The cELISA method was evaluated using standard curves made in both assay buffer and chicken liver extract The results demonstrated that standard curves made in assay buffer could be used for the cELISA. HPLC vs. cELISA results were obtained during 2 studies; the 1st study used spiked chicken liver tissue, and the 2nd study used both spiked chicken liver tissue and incurred levels of Hal in chicken liver tissue. There was good agreement in the results obtained by HPLC and cELISA. However, in most cases the recovery was higher using the cELISA method than with the HPLC method. In addition, the cELISA method does not require the use of organic solvents. Thus, the cELISA method could be used as a screening method for the anal. of Hal in chicken liver tissue.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1998:169290 CAPLUS
DOCUMENT NUMBER: 128:278527
ORIGINAL REFERENCE NO.: 128:54985a,54988a
TITLE: Halofuginone: a novel antifibrotic therapy
AUTHOR(S): Pines, M.; Nagler, A.
CORPORATE SOURCE: The Volcani Center, Institute of Animal Science, Agricultural Research Organization, Bet Dagan, 50250, Israel
SOURCE: General Pharmacology (1998), 30(4), 445-450
CODEN: GEPHDP; ISSN: 0306-3623
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with .apprx.60 refs. 1. Fibrosis is characterized by extracellular matrix deposition, of which collagen type I is the major constituent. The progressive accumulation of connective tissue resulted in destruction of normal tissue architecture and function. 2. Fibrosis is a common response to various insults or injuries and can be the outcome of any perturbation in the cellular function of any tissue. 3. Halofuginone was found to inhibit collagen α1(I) gene expression and collagen synthesis in a variety of cell cultures including human fibroblasts derived from patients with excessive skin collagen type I synthesis. 4. Halofuginone was found to inhibit collagen α1(I) gene expression and collagen synthesis in animal models characterized by excessive deposition of collagen. In these models, fibrosis was induced in various tissues such as skin, liver, lung, etc. Halofuginone was injected i.p., added to the foodstuff or applied locally. 5. Halofuginone decreased skin collagen in a chronic graft-vs.-host disease patient. 6. The ability of extremely low concns. of halofuginone to inhibit collagen α1(I) synthesis specifically and transiently at the transcriptional level suggests that this material fulfills the criteria for a successful and effective anti-fibrotic therapy.
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1997:592832 CAPLUS
DOCUMENT NUMBER: 127:257573
ORIGINAL REFERENCE NO.: 127:50192h,50193a
TITLE: Halofuginone, a specific inhibitor of collagen type I synthesis, prevents dimethylnitrosamine-induced liver cirrhosis
AUTHOR(S): Pines, Mark; Knopov, Viktor; Genina, Olga; Lavelin, Irina; Nagler, Arnon
CORPORATE SOURCE: The Volcani Center, Institute of Animal Science, Agricultural Research Organization, Bet Dagan, 50250, Israel
SOURCE: Journal of Hepatology (1997), 27(2), 391-398
CODEN: JOHEEC; ISSN: 0168-8278
PUBLISHER: Munksgaard
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hepatic cirrhosis is characterized by excessive deposition of collagen, resulting from an increase in type I collagen gene transcription. The authors evaluated the effect of halofuginone - a specific inhibitor of collagen type α1(I) gene expression - on dimethylnitrosamine (DMN)-induced liver fibrosis/cirrhosis in rats. Fibrosis was induced by i.p. injection of DMN. Halofuginone (5 mg/kg) was added to the diet. Collagen was stained with Sirius red and collagen α1(I) gene expression was evaluated by in situ hybridization. In control rats, a low level of collagen α1(I) gene expression was observed A high dose of DMN (1%) caused severe fibrosis, as indicated by induction of collagen α1(I) gene expression and increased liver collagen content. Addition of halofuginone before the onset of fibrosis, almost completely prevented the increase in collagen type I gene expression and resulted in lower liver collagen content. Moreover, halofuginone partially prevented the marked decrease in liver weight and reduced the mortality rate. At a lower dose of DMN (0.25%), which causes mild fibrosis, halofuginone prevented the increase in collagen α1(I) gene expression, prevented the increase in liver collagen deposition and reduced plasma alkaline phosphatase activity, all of which are characteristic of liver fibrosis/cirrhosis. These results suggest that halofuginone can be used as an important tool to understand the regulation of the collagen α1(I) gene and may become a novel and promising antifibrotic agent for liver fibrosis/cirrhosis.
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1996:393040 CAPLUS
DOCUMENT NUMBER: 125:85078
ORIGINAL REFERENCE NO.: 125:16047a,16050a
TITLE: Residues of halofuginone in tissues of broilers fed mixed feeds containing calcium halofuginone polystyrene sulfonate
AUTHOR(S): Ikezawa, Akito; Sato, Yasuhiko; Saito, Norio; Ishibashi, Takayuki; Yamaguchi, Yasuki; Kazama, Reiko; Obigane, Shigeto
CORPORATE SOURCE: Fukuoka Fertilizer and Feed Inspection Station, Fukuoka, Japan
SOURCE: Shiryo Kenkyu Hokoku (Tokyo Hishiryo Kensasho) (1996), 21, 173-180
CODEN: SHTKD3; ISSN: 0286-4746
PUBLISHER: Norin Suisansho Tokyo Hishiryo Kensasho
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB Mixed feeds containing calcium halofuginone polystyrene-sulfonate (HPS) at

concns. authorized for safe use in Japan (40g/ton) were given to broilers by free feeding for 28 days. Afterward, a feed free of HPS was given for 7 days. After slaughter, halofuginone was not detected from any meat tissues of broilers when examined by high performance liquid chromatog., but it was detected in the liver.

L4 ANSWER 15 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1996:373869 CAPLUS
DOCUMENT NUMBER: 125:56510
ORIGINAL REFERENCE NO.: 125:10881a,10884a
TITLE: Detection of halofuginone residues in chicken serum by a monoclonal-based immunoassay and high-performance liquid chromatography
AUTHOR(S): Beier, Ross C.; Rowe, Loyd D.; Nasr, Magdy I. Abd El-Aziz; Elissalde, Marcel H.; Rose, Beate G.; Stanker, Larry H.
CORPORATE SOURCE: US Department Agriculture, Agricultural Research Service, College Station, TX, 77845-9594, USA
SOURCE: Food and Agricultural Immunology (1996), 8(1), 11-17
CODEN: FAIMEZ; ISSN: 0954-0105
PUBLISHER: Carfax
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This study evaluated the usefulness of determining halofuginone (Hal) in chicken serum with a competitive ELISA (cELISA). If a 4-day withdrawal time could be determined by serum Hal levels, the method would greatly improve on the HPLC methods currently used for Hal detection in liver tissue. A modification of a previously developed HPLC method was used to validate the cELISA anal. of Hal in chicken serum. A serum matrix effect that afforded a higher sensitivity of the cELISA for Hal in chicken serum than in assay buffer or in highly diluted serum was observed The sensitivity of the cELISA method improved when used in more concentrated serum. The chicken serum samples were evaluated by cELISA, using a standard curve obtained in control chicken serum diluted 2-fold with assay buffer. Incurred levels of Hal in broiler chickens fed Hal-HBr-treated feed were detected in serum after withdrawal times of 2 and 6 h. At and after 24 h, the residues were not detected by immunoassay with a detection limit of 0.52 ppb or by HPLC with detection limit of 0.86 ppb. The instability of Hal in acidified serum and its potential for methanolysis in the HPLC method were overcome by using the cELISA methodol. Although the determination of Hal in chicken serum by immunoassay is fast, requiring no clean-up steps, chicken serum cannot be used to determine the required 4-day withdrawal time in broiler chickens because of the lack of residues in the serum at and after 24 h.

L4 ANSWER 16 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1994:578121 CAPLUS
DOCUMENT NUMBER: 121:178121
ORIGINAL REFERENCE NO.: 121:32343a,32346a
TITLE: Levels of coccidiostats in chicken tissues after feeding medicated feed
AUTHOR(S): Tarbin, J. A.; Chapman, S.; Farrington, W. H. H.; Patey, A. L.; Shearer, G.
CORPORATE SOURCE: Food Saf. Dir., Minist. Agric. Fish. and Food, Food Sci. Lab., Norwich, NR4 7UQ, UK
SOURCE: Residues Vet. Drugs Food, Proc. EuroResidue Conf., 2nd (1993), Volume 2, 655-8. Editor(s): Haagsma, N.; Ruiter, A.; Czedik-Eysenberg, Peter B. Utrecht Univ. Fac. Vet. Med.: Utrecht, Neth.
CODEN: 60CDAT

DOCUMENT TYPE: Conference
LANGUAGE: English
AB Over a period of 46 days, chickens were fed monensin, narasin, salinomycin and halofuginone at the com. dose. Tissues of birds slaughtered after 0, 1, 2 and 3 days withdrawal were analyzed for residues. Monensin, narasin and salinomycin were quantified by HPTLC. Halofuginone was quantified by HPLC. Residues of all four coccidiostats were found in all tissues analyzed after 0 days withdrawal. Levels of monensin, narasin and salinomycin decreased to below the detection limit after 1 day withdrawal. Levels of halofuginone reduced to below 0.010 mg kg-1 after 1 day withdrawal in muscle tissue.

L4 ANSWER 17 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1992:424899 CAPLUS
DOCUMENT NUMBER: 117:24899
ORIGINAL REFERENCE NO.: 117:4481a,4484a
TITLE: Tolerances for residues of new animal drugs in food; halofuginone hydrobromide
CORPORATE SOURCE: United States Food and Drug Administration, Rockville, MD, 20857, USA
SOURCE: Federal Register (1992), 57(97), 21209, 19 May 1992
CODEN: FEREAC; ISSN: 0097-6326
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The marker residue for Stenorol (halofuginone-HBr) in turkey liver is amended to 0.13 ppm, under the Federal Food, Drug, and Cosmetic Act.

L4 ANSWER 18 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1992:127159 CAPLUS
DOCUMENT NUMBER: 116:127159
ORIGINAL REFERENCE NO.: 116:21505a,21508a
TITLE: Simple determination of halofuginone in chicken tissue by high performance liquid chromatography
AUTHOR(S): Yamamoto, Yuzo; Hashiguchi, Reiko; Araki, Keiko; Kushima, Hirofumi
CORPORATE SOURCE: Miyazaki Prefect. Inst. Public Health Environ., Miyazaki, 889-21, Japan
SOURCE: Shokuhin Eiseigaku Zasshi (1991), 32(5), 444-7
CODEN: SKEZAP; ISSN: 0015-6426
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB Halofuginone in chicken tissue is determined by extraction with acetate buffer-MeOH, concentration, extraction with AcOEt and HPLC using MeCN-acetate buffer-H2O containing tetra-n-BuNBr. The recoveries in chicken muscle, liver and egg were 87, 64 and 64%, resp.

L4 ANSWER 19 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1991:162567 CAPLUS
DOCUMENT NUMBER: 114:162567
ORIGINAL REFERENCE NO.: 114:27479a,27482a
TITLE: Tolerances for residues of new animal drugs in food; halofuginone hydrobromide
CORPORATE SOURCE: United States Food and Drug Administration, Rockville, MD, 20857, USA
SOURCE: Federal Register (1991), 56(41), 8710-11, 1 Mar 1991
CODEN: FEREAC; ISSN: 0097-6326
DOCUMENT TYPE: Journal

LANGUAGE: English
AB Stenorol (halofuginone-HBr) may be used in poultry feed for the prevention of coccidiosis, under the Federal Food, Drug, and Cosmetic Act, and tolerances of 0.16 and 0.1 ppm are established for parent halofuginone-HBr in livers of broilers and turkeys, resp. These marker residue concns. correspond to total residue concns. of 0.3 ppm in liver.

L4 ANSWER 20 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1989:513897 CAPLUS
DOCUMENT NUMBER: 111:113897
ORIGINAL REFERENCE NO.: 111:19095a,19098a
TITLE: Animal drugs, feeds, and related products; halofuginone
CORPORATE SOURCE: United States Food and Drug Administration, Rockville, MD, 20857, USA
SOURCE: Federal Register (1989), 54(127), 28051-3, 5 Jul 1989
CODEN: FEREAC; ISSN: 0097-6326
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Halofuginone-HBr (I) type A medicated articles may be used to prepare medicated feeds containing 1.36-2.72 g I/ton for prevention of coccidiosis in turkeys, under the Federal Food, Drug, and Cosmetic Act. The tolerance for I in liver is 0.1 ppm, which corresponds to 0.3 ppm total I in liver. The safe concns. of I in turkey are: muscle 0.1, liver 0.3, and skin with s.c. fat 0.2 ppm.

L4 ANSWER 21 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1986:532322 CAPLUS
DOCUMENT NUMBER: 105:132322
ORIGINAL REFERENCE NO.: 105:21337a,21340a
TITLE: Residue test of calcium halofuginone polystyrenesulfonate in broiler chickens
AUTHOR(S): Murano, Takako; Uchino, Takeshi; Ino, Rinpei
CORPORATE SOURCE: Div. Poult. Farming, Livest. Cent. Chiba Prefect., 289-11, Japan
SOURCE: Kenkyu Hokoku - Chiba-ken Chikusan Senta (1985), (9), 31-7
CODEN: KHCSDO; ISSN: 0386-5673
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB Feeds which contained 40, 80, and 120 ppm Ca halofuginone poly(styrenesulfonate) (CHP) were repeatedly administered to broiler chickens and the residual rates of CHP in several organs were studied. The concns. of CHP in liver, kidney, skin, muscle, fat and blood were below detection limits 7, 7, 5, 3, 2 and 2 days after repeated administration at all concns. of CHP, resp. CHP apparently did not remain in any organ of broiler chickens for a long time.

L4 ANSWER 22 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1985:540456 CAPLUS
DOCUMENT NUMBER: 103:140456
ORIGINAL REFERENCE NO.: 103:22485a,22488a
TITLE: Tolerances for residues of new animal drugs in food; new animal drugs for use in animal feeds; halofuginone hydrobromide
AUTHOR(S): Gabuten, Adriano
CORPORATE SOURCE: Cent. Vet. Med., Food Drug Adm., Rockville, MD, 20857, USA
SOURCE: Federal Register (1985), 50(162), 33718-19, 21 Aug 1985
CODEN: FEREAC; ISSN: 0097-6326

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Halofuginone-HBr [64924-67-0] may be fed to broiler chickens to prevent coccidiosis, and tolerances of 0.1 ppm for parent halofuginone [55837-20-2] and 0.3 ppm for total residues is established for liver, under the Federal Food, Drug, and Cosmetic Act. The feed may contain 2.72 g halofuginone-Hbr/ton, and must be withdrawn 4 days before slaughter.

L4 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1984:405595 CAPLUS
DOCUMENT NUMBER: 101:5595
ORIGINAL REFERENCE NO.: 101:967a,970a
TITLE: Collaborative study of a method for the determination of residues of halofuginone in chicken tissue
CORPORATE SOURCE: Analytical Methods Committee, R. Soc. Chem., UK
SOURCE: Analyst (Cambridge, United Kingdom) (1984), 109(2), 171-4
CODEN: ANALAO; ISSN: 0003-2654
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The halofuginone [55837-20-2] is extracted as the free base with EtOAc after digestion of chicken tissues with trypsin and then partitioned into an aqueous NH4OAc buffer. After further clean-up and concentration using a Sep-Pak C18 cartridge, the extract is examined by high-performance liquid chromatog. using a reversed-phase column and a UV detector. The procedure was tested by carrying out procedural recoveries from spiked samples and also by a collaborative exercise using samples of tissues from birds fed on a diet containing halofuginone. The efficiency of the extraction procedure was assessed by using samples of a chicken that had been fed with 14C-labeled halofuginone.

L4 ANSWER 24 OF 24 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1979:568302 CAPLUS
DOCUMENT NUMBER: 91:168302
ORIGINAL REFERENCE NO.: 91:27021a,27024a
TITLE: Factors influencing the assessment of anticoccidial activity in cell culture
AUTHOR(S): Latter, Victoria S.; Wilson, R. G.
CORPORATE SOURCE: Wellcome Res. Lab., Beckenham/Kent, BR3 3BS, UK
SOURCE: Parasitology (1979), 79(1), 169-75
CODEN: PARAAE; ISSN: 0031-1820
DOCUMENT TYPE: Journal
LANGUAGE: English
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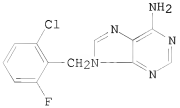

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AB A comparative study was made of the factors influencing the assessment of anticoccidial potency in vitro against Eimeria tenella using established

anticoccidials and arprinocid (I) [55779-18-5] and some of its analogs. Drugs whose potency depended upon medium composition were amprolium [121-25-5], lasalocid [11054-70-9], and halofuginone [55837-20-2]. There was a difference in strain sensitivity with robenidine [25875-51-8]. Host cell type had an important effect on potency of monensin [17090-79-8], decoquinate [18507-89-6], and I and its analogs. I was active in chick liver cell systems but totally inactive in chick kidney cell systems, although its N-oxide was active in both cell types. I-containing medium, conditioned by supporting the growth of chick embryo liver cell cultures, had an anticoccidial effect on E. tenella growing in chick kidney cells. Thus, the anticoccidial activity of I in the chick is due to a metabolite.

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NEWS 21	APR 28	EMBASE Controlled Term thesaurus enhanced
NEWS 22	APR 28	IMSRESEARCH reloaded with enhancements
NEWS 23	MAY 30	INPAFAMDB now available on STN for patent family searching

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 NEWS 25  JUN 06  EPFULL enhanced with 260,000 English abstracts
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 NEWS 27  JUN 13  USPATFULL and USPAT2 updated with 11-character
                  patent numbers for U.S. applications
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=> s halofuginone and (liver or hepatocyte) and regenerat?
L1            7 HALOFUGINONE AND (LIVER OR HEPATOCYTE) AND REGENERAT?

=> d l1 ibib abs l-7

L1   ANSWER 1 OF 7     MEDLINE on STN
ACCESSION NUMBER:   2008333929     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 18458672
TITLE:              Halofuginone upregulates the expression of
                    heparanase in thioacetamide-induced liver
                    fibrosis in rats.
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AUTHOR: Ohayon Olga; Mawasi Nidal; Pevzner Anna; Tryvitz Ana; Gildor Tsvia; Pines Mark; Rojkind Marcos; Paizi Melia; Spira Gadi

CORPORATE SOURCE: Department of Anatomy and Cell Biology, The Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel.

CONTRACT NUMBER: AA09231 (United States NIAAA)
R01 AA10541 (United States NIAAA)

SOURCE: Laboratory investigation; a journal of technical methods and pathology, (2008 Jun) Vol. 88, No. 6, pp. 627-33. Electronic Publication: 2008-05-05. Journal code: 0376617. E-ISSN: 1530-0307.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, N.I.H., EXTRAMURAL) (RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200806

ENTRY DATE: Entered STN: 24 May 2008
Last Updated on STN: 11 Jun 2008
Entered Medline: 10 Jun 2008

AB Advanced hepatic fibrosis is characterized by excessive extracellular matrix deposition, where collagen and proteoglycans are the main constituents of scar tissue. In previous studies, we showed that heparanase, a heparan sulfate-degrading enzyme, and vascular endothelial growth factor (VEGF) play an important role during liver development and remodeling. In this communication, we investigated the relationship between heparanase and VEGF in thioacetamide-induced liver fibrosis in rats. Our study shows that heparanase mRNA expression levels correlate with those of VEGF during the induction and recovery stages of liver fibrosis. We further demonstrated that treating fibrotic rat livers with halofuginone (HF), a multipotent antifibrogenic drug, and subsequently subjecting them to hydrodynamics-based transfection with human VEGF-165 resulted in elevated expression of heparanase mRNA. Moreover, these rats demonstrated an improved capacity to regenerate following 70% partial hepatectomy. In vitro, HF stimulated heparanase and VEGF mRNA expression in hepatic stellate cells. Taken together, our results suggest that in addition to the known multiple functions of HF, it also enhances heparanase and VEGF expression and promotes liver regeneration. Accordingly, HF seems to possess ideal properties required to become an excellent antifibrogenic agent in humans.

L1 ANSWER 2 OF 7 MEDLINE on STN

ACCESSION NUMBER: 2006230955 MEDLINE

DOCUMENT NUMBER: PubMed ID: 16508789

TITLE: Involvement of the tyrosine phosphatase early gene of liver regeneration (PRL-1) in cell cycle and in liver regeneration and fibrosis effect of halofuginone.

AUTHOR: Gnainsky Yulia; Spira Gadi; Paizi Melia; Bruck Raffael; Nagler Arnon; Genina Olga; Taub Rebbeca; Halevy Orna; Pines Mark

CORPORATE SOURCE: Institute of Animal sciences , Volcani Center , P.O. Box 6 , 50250 Bet Dagan , Israel.

SOURCE: Cell and tissue research, (2006 Jun) Vol. 324, No. 3, pp. 385-94. Electronic Publication: 2006-03-01. Journal code: 0417625. ISSN: 0302-766X.

PUB. COUNTRY: Germany: Germany, Federal Republic of

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200704
ENTRY DATE: Entered STN: 27 Apr 2006
Last Updated on STN: 11 Apr 2007
Entered Medline: 10 Apr 2007

AB Tyrosine phosphatase PRL-1 is one of the immediate-early genes up-regulated during liver regeneration and is apparently involved in cell proliferation. Previously, we have demonstrated that halofuginone, an inhibitor of collagen type I synthesis, prevents liver fibrosis and improves cirrhotic liver regeneration. In this study, we evaluated the effect of halofuginone on PRL-1 expression, its cellular localization in vitro and during liver regeneration, and fibrosis progression in vivo. In culture, halofuginone increased PRL-1 expression in primary rat hepatocytes and in hepatocellular carcinoma (HCC) cell lines, the former being more sensitive to halofuginone. The halofuginone-dependent increase in PRL-1 gene expression was correlated with an increase in the transcription factor early growth response-1 (Egr-1) and inversely correlated with the inhibition of cell proliferation. Halofuginone arrested HepG2 and Huh7 cell lines at the G1 phase, whereas Hep3B cells were arrested at G2/M, probably because of a reduction in the synthesis of cyclins D1 and B1 in all HCC cells and increased cyclin A in Hep3B cells. Halofuginone also affected the PRL-1 sub-cellular localization that was cell-cycle-dependent. In addition, halofuginone augmented PRL-1 expression in the remnant liver after partial hepatectomy and in chemically induced fibrosis in rats; this was accompanied by increased expression of insulin-like growth factor binding protein 1 (IGFBP-1), another immediate-early gene of regeneration. The regulation of the expression of the early genes of regeneration such as PRL-1 and IGFBP-1 is thus part of the mode of action of halofuginone and results in the prevention of liver fibrosis and improved cirrhotic liver regeneration.

L1 ANSWER 3 OF 7 MEDLINE on STN
ACCESSION NUMBER: 2002422182 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12175628
TITLE: Halofuginone, a collagen type I inhibitor improves liver regeneration in cirrhotic rats.
AUTHOR: Spira Gadi; Mawasi Nidal; Paizi Melia; Anbinder Natali; Genina Olga; Alexiev Rosaly; Pines Mark
CORPORATE SOURCE: Department of Anatomy and Cell Biology, The Bruce Rappaport Faculty of Medicine, Rappaport Family Institute for Research in the Medical Sciences, Technion, Haifa, Israel.. spira@tx.technion.ac.il
SOURCE: Journal of hepatology, (2002 Sep) Vol. 37, No. 3, pp. 331-9.
Journal code: 8503886. ISSN: 0168-8278.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 15 Aug 2002
Last Updated on STN: 8 Apr 2003
Entered Medline: 7 Apr 2003

AB BACKGROUND/AIMS: Hepatic fibrosis involves excess deposition of extracellular connective tissue of which collagen type I fibers form the

predominant component. Left untreated it develops into cirrhosis, often linked with hepatocellular carcinoma. Owing to the fact that cirrhotic liver regeneration is impaired, resection of hepatocellular carcinoma associated with cirrhosis is questionable. The aim of the present study was to determine the potential of halofuginone, a collagen type I inhibitor, in improving liver regeneration in cirrhotic rats. METHODS: Partial hepatectomy (70%) was performed in thioacetamide-induced cirrhotic rats fed a halofuginone-containing diet. Liver regeneration was monitored by mass and proliferating cell nuclear antigen. The Ishak staging system and hydroxyproline content were used to evaluate the level of fibrosis. RESULTS: Halofuginone administered prior to and following partial hepatectomy did not inhibit normal liver regeneration despite the reduced levels of collagen type I mRNA. When given to rats with established fibrosis, it caused a significant reduction in alpha smooth muscle actin, TIMP-2, collagen type I gene expression and collagen deposition. Such animals demonstrated improved capacity for regeneration. CONCLUSIONS: Halofuginone may prove useful in improving survival of patients with hepatocellular carcinoma and cirrhosis undergoing surgical resection.

L1 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2008:620354 CAPLUS
TITLE: Halofuginone upregulates the expression of heparanase in thioacetamide-induced liver fibrosis in rats
AUTHOR(S): Ohayon, Olga; Mawasi, Nidal; Pevzner, Anna; Tryvitz, Ana; Gildor, Tsvia; Pines, Mark; Rojkind, Marcos; Paizi, Melia; Spira, Gadi
CORPORATE SOURCE: Department of Anatomy and Cell Biology, The Bruce Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel
SOURCE: Laboratory Investigation (2008), 88(6), 627-633
CODEN: LAINAW; ISSN: 0023-6837
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Advanced hepatic fibrosis is characterized by excessive extracellular matrix deposition, where collagen and proteoglycans are the main constituents of scar tissue. In previous studies, we showed that heparanase, a heparan sulfate-degrading enzyme, and vascular endothelial growth factor (VEGF) play an important role during liver development and remodeling. In this communication, we investigated the relationship between heparanase and VEGF in thioacetamide-induced liver fibrosis in rats. Our study shows that heparanase mRNA expression levels correlate with those of VEGF during the induction and recovery stages of liver fibrosis. We further demonstrated that treating fibrotic rat livers with halofuginone (HF), a multipotent antifibrogenic drug, and subsequently subjecting them to hydrodynamics-based transfection with human VEGF-165 resulted in elevated expression of heparanase mRNA. Moreover, these rats demonstrated an improved capacity to regenerate following 70% partial hepatectomy. In vitro, HF stimulated heparanase and VEGF mRNA expression in hepatic stellate cells. Taken together, our results suggest that in addition to the known multiple functions of HF, it also enhances heparanase and VEGF expression and promotes liver regeneration. Accordingly, HF seems to possess ideal properties required to become an excellent antifibrogenic agent in humans. Laboratory Investigation (2008) 88, 627-633; doi:10.1038/labinvest.2008.30; published online 5 May 2008.

L1 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:390410 CAPLUS

DOCUMENT NUMBER: 145:369747
TITLE: Involvement of the tyrosine phosphatase early gene of liver regeneration (PRL-1) in cell cycle and in liver regeneration and fibrosis effect of halofuginone
AUTHOR(S): Gnainsky, Yulia; Spira, Gadi; Paizi, Melia; Bruck, Raffael; Nagler, Arnon; Genina, Olga; Taub, Rebbeca; Halevy, Orna; Pines, Mark
CORPORATE SOURCE: Institute of Animal sciences, Volcani Center, Bet Dagan, 50250, Israel
SOURCE: Cell & Tissue Research (2006), 324(3), 385-394
CODEN: CTSRCS; ISSN: 0302-766X
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tyrosine phosphatase PRL-1 is one of the immediate-early genes up-regulated during liver regeneration and is apparently involved in cell proliferation. Previously, we have demonstrated that halofuginone, an inhibitor of collagen type I synthesis, prevents liver fibrosis and improves cirrhotic liver regeneration. In this study, we evaluated the effect of halofuginone on PRL-1 expression, its cellular localization in vitro and during liver regeneration, and fibrosis progression in vivo. In culture, halofuginone increased PRL-1 expression in primary rat hepatocytes and in hepatocellular carcinoma (HCC) cell lines, the former being more sensitive to halofuginone. The halofuginone-dependent increase in PRL-1 gene expression was correlated with an increase in the transcription factor early growth response-1 (Egr-1) and inversely correlated with the inhibition of cell proliferation. Halofuginone arrested HepG2 and Huh7 cell lines at the G1 phase, whereas Hep3B cells were arrested at G2/M, probably because of a reduction in the synthesis of cyclins D1 and B1 in all HCC cells and increased cyclin A in Hep3B cells. Halofuginone also affected the PRL-1 sub-cellular localization that was cell-cycle-dependent. In addition, halofuginone augmented PRL-1 expression in the remnant liver after partial hepatectomy and in chemical induced fibrosis in rats; this was accompanied by increased expression of insulin-like growth factor binding protein 1 (IGFBP-1), another immediate-early gene of regeneration. The regulation of the expression of the early genes of regeneration such as PRL-1 and IGFBP-1 is thus part of the mode of action of halofuginone and results in the prevention of liver fibrosis and improved cirrhotic liver regeneration.

REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2004:387228 CAPLUS
DOCUMENT NUMBER: 140:386059
TITLE: Quinazolinone compositions for regulation of gene expression related to pathological processes
INVENTOR(S): Pines, Mark; Nagler, Arnon; Yarkoni, Shai
PATENT ASSIGNEE(S): State of Israel, Ministry of Agriculture, Israel; Hadasit Medical Research Services and Development Ltd.; Collgard Biopharmaceuticals Ltd.
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004039308	A2	20040513	WO 2003-IL900		20031030
WO 2004039308	A3	20040708			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2504388	A1	20040513	CA 2003-2504388		20031030
AU 2003278579	A1	20040525	AU 2003-278579		20031030
EP 1558261	A2	20050803	EP 2003-769875		20031030
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
JP 2006504769	T	20060209	JP 2004-547952		20031030
US 20060258692	A1	20061116	US 2006-533371		20060601
PRIORITY APPLN. INFO.:			US 2002-422487P	P	20021031
			WO 2003-IL900	W	20031030

OTHER SOURCE(S): MARPAT 140:386059

AB The invention discloses pharmaceutical compns. for modifying gene expression in a pathol. process, thereby preventing or ameliorating the process. More particularly the compns. comprise quinazolinones, especially halofuginone, for inhibiting or preventing alterations in gene expression during fibrosis. The invention particularly relates to pharmaceutical compns. for improving the regeneration of cirrhotic liver.

L1 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER:	2002:600553 CAPLUS
DOCUMENT NUMBER:	138:379131
TITLE:	Halofuginone, a collagen type I inhibitor improves liver regeneration in cirrhotic rats
AUTHOR(S):	Spira, Gadi; Mawasi, Nidal; Paizi, Melia; Anbinder, Natali; Genina, Olga; Alexiev, Rosaly; Pines, Mark
CORPORATE SOURCE:	Rappaport Family Institute for Research in the Medical Sciences, The Bruce Rappaport Faculty of Medicine, Department of Anatomy and Cell Biology, Technion, Haifa, Israel
SOURCE:	Journal of Hepatology (2002), 37(3), 331-339 CODEN: JOHEEC; ISSN: 0168-8278
PUBLISHER:	Elsevier Science Ltd.
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Hepatic fibrosis involves excess deposition of extracellular connective tissue of which collagen type I fibers form the predominant component. Left untreated it develops into cirrhosis, often linked with hepatocellular carcinoma. Owing to the fact that cirrhotic liver regeneration is impaired, resection of hepatocellular carcinoma associated with cirrhosis is questionable. The aim of the present study was to determine the potential of halofuginone, a collagen type I inhibitor, in improving liver regeneration in cirrhotic rats. Partial hepatectomy (70%) was performed in thioacetamide-induced cirrhotic rats fed a halofuginone-containing diet. Liver regeneration was monitored by mass and proliferating cell nuclear antigen. The Ishak staging system and

hydroxyproline content were used to evaluate the level of fibrosis. Halofuginone administered prior to and following partial hepatectomy did not inhibit normal liver regeneration despite the reduced levels of collagen type I mRNA. When given to rats with established fibrosis, it caused a significant reduction in α smooth muscle actin, TIMP-2, collagen type I gene expression and collagen deposition. Such animals demonstrated improved capacity for regeneration. Thus, halofuginone may prove useful in improving survival of patients with hepatocellular carcinoma and cirrhosis undergoing surgical resection.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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